Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

An analysis of the short- and long-term cost-effectiveness of starting biphasic insulin aspart 30 in insulin-naïve people with poorly controlled type 2 diabetes

Asrul Akmal Shafie [a], *Vishal Gupta* [b], *Ranya Baabbad* [c], *Eva Hammerby* [d], *Philip Home* [e,*]

[a] *Universiti Sains Malaysia, Georgetown, Penang, Malaysia*
[b] *Jaslok Hospital and Research Centre, Mumbai, India*
[c] *Pharmacoeconomics Centre of KSMC, Riyadh, Saudi Arabia*
[d] *Novo Nordisk A/S, Søborg, Denmark*
[e] *Newcastle University, Newcastle upon Tyne, UK*

ARTICLE INFO

Article history:
Received 25 February 2014
Received in revised form
27 June 2014
Accepted 30 August 2014
Available online 16 September 2014

Keywords:
A_1chieve
Type 2 diabetes mellitus
Cost-effectiveness
Biphasic insulin aspart 30

ABSTRACT

Aim: This study aimed to assess the cost-effectiveness of starting insulin therapy with biphasic insulin aspart 30 (BIAsp 30) in people with type 2 diabetes inadequately controlled on oral glucose-lowering drugs in Saudi Arabia, India, Indonesia, and Algeria.

Methods: The IMS CORE Diabetes Model was used to evaluate economic outcomes associated with starting BIAsp 30, using baseline characteristics and treatment outcomes from the A_1chieve study. Time horizons of 1 and 30 years were applied, with country-specific costs for complications, therapies, and background mortality. Incremental cost-effectiveness ratios (ICERs) are expressed as cost per quality-adjusted life-year (QALY) in local currencies, USD, and fractions of local GDP per capita (GDPc). Cost-effectiveness was pre-defined using the World Health Organization definition of <3.0 times GDPc. Comprehensive sensitivity analyses were performed.

Results: In the primary 30-year analyses, starting BIAsp 30 was associated with a projected increase in life expectancy of >1 year and was highly cost-effective, with ICERs of −0.03 (Saudi Arabia), 0.25 (India), 0.48 (India), 0.47 (Indonesia), and 0.46 (Algeria) GDPc/QALY. The relative risk of developing selected complications was reduced in all countries. Sensitivity analyses including cost of self-monitoring, treatment costs, and deterioration of glucose control with time showed the results to be robust. In a 1-year analysis, ICER per QALY gained was still cost-effective or highly cost-effective.

Conclusion: Starting BIAsp 30 in people with type 2 diabetes in the A_1chieve study was found to be cost-effective across all country settings at 1- and 30-year time horizons, and usefully increased predicted life expectancy.

* Corresponding author. Tel.: +44 191 208 7154; fax: +44 191 222 0723.
E-mail address: philip.home@newcastle.ac.uk (P. Home).

http://dx.doi.org/10.1016/j.diabres.2014.08.024
0168-8227/

1. Introduction

The worldwide prevalence of diabetes is steadily increasing, and is expected to reach 592 million by 2035 [1]. Global diabetes-related expenditure, estimated at USD548 billion in 2013, is expected to increase to USD627 billion by 2035 [1]. The International Diabetes Federation estimates that 80% of people with diabetes live in low- and middle-income countries where local health-care systems are often not equipped to deal with the economic burden of diabetes [2]. Newly developed countries also have high diabetes prevalence.

In developing and recently developed countries, many people with diabetes are diagnosed late and may already have diabetes-related complications, resulting in significant costs for individuals and families where government-funded healthcare social security is low or absent. People of working age are especially affected, with consequences for the economic potential of the countries [1]. Successful management of diabetes includes control of high glucose levels [2,3]. However, many people with type 2 diabetes mellitus (T2DM) are not achieving the generally recommended levels for good glycaemic control ($HbA_{1c} < 7.0\%$ [<53 mmol/mol]) [2–5].

Analyses of randomised clinical trials (RCTs) [6,7] and data from non-interventional studies [4,5,8] confirm that beginning insulin analogues in people taking glucose-lowering drugs (OGLDs) alone is associated with clinically significant improvements in glucose control while improving quality of life. Furthermore, there is evidence to support biphasic insulin aspart 30 (BIAsp 30) as a cost-effective treatment option in a number of western and developed countries [9–11].

Evaluation of how health-care funds should be spent to maximise health benefits requires assessment of the economic impact of diabetes interventions. Because of the progressive nature of diabetes and the complexity of the clinical outcomes, health-economic (HE) data modelling is helpful in estimating the effects of an intervention on health consequences and costs. These models can bring together data from a variety of different sources including RCTs, observational studies, case registries, public health statistics, and quality-of-life surveys, simulating disease progression and related costs through time in a population. In rapidly developing and recently developed countries where health-care costs are diverse, data from observational studies can be of use in HE modelling by reflecting actual outcomes in clinical practice, especially where there is a paucity of RCT data for these populations [12–14].

A_1chieve was a very large observational study conducted in countries across Asia, Africa, Eastern Europe, and Latin America, designed to evaluate the safety and clinical effectiveness of insulin analogues in people with T2DM in clinical practice [4]. It thus provides an opportunity to explore how the insulin analogues performed in diverse, heterogeneous populations and to conduct cost-effectiveness analyses in non-western populations. In turn, this may help the evolution of diabetes guidelines and enable the optimal allocation of scarce health-care resources. Furthermore, the prospective use of the globally validated EQ-5D instrument provides a unique opportunity to base the health-related quality of life (HRQoL) data used as input in the HE model on answers from the same population as the clinical outcomes are observed. The aim of the present analysis is to assess the long- and short-term cost-effectiveness of starting BIAsp 30 in people with T2DM poorly controlled on OGLDs applying the specific EQ-5D and clinical outcome data collected during the A_1chieve study.

2. Participants and methods

2.1. A_1chieve data collection

A_1chieve was a 24-week, international, non-interventional, observational study in insulin-naïve and insulin-experienced people with T2DM from 28 countries starting treatment with BIAsp 30, insulin detemir, or insulin aspart (all Novo Nordisk, Copenhagen, Denmark) ± OGLDs in routine clinical practice. Details of the study design and methods and global primary data have been published elsewhere [4,15]. In summary, data were collected on clinical effectiveness and adverse events at routine clinical visits (baseline, 12 and 24·weeks). Participants were asked to complete the EQ-5D questionnaire, used for self-assessment of HRQoL, at baseline and week 24 [15].

2.2. Simulation cohort

The cost-effectiveness analysis used clinical data from the A_1chieve study for the measurement of health outcomes. Data were included for people being treated for diabetes with OGLDs alone at pre-study and starting BIAsp 30 at baseline, in most cases keeping at least part of the OGLD treatment. To secure reliable estimates and for the analysis to be representative for the average population, only countries where more than 100 insulin-naïve people started BIAsp 30 were included. An HbA_{1c} result at both baseline and end of study was also required. These criteria result in study populations from Saudi Arabia ($n = 901$), India ($n = 7546$), and Indonesia ($n = 153$), and three North African countries grouped together (Algeria, Tunisia, and Morocco; $n = 279$), analysed using economic data from Algeria. The prevalence of diabetes has risen dramatically in these neighbouring countries in recent years and they have experienced similar rapid economic development and changes in lifestyle that endorse their assignment as a single population, defined specifically by treatment choice, for this analysis [16]. Baseline characteristics of the defined populations, and changes in blood-glucose control, body mass index, plasma lipids, systolic blood pressure, hypoglycaemia, and EQ-5D-based HRQoL are shown in Table 1.

The clinical and economic costs of starting BIAsp30 (with or without changes to OGLDs) in each country were projected over a 30-year time horizon for the base-case using the IMS CORE Diabetes Model (version 8.5; Basel, Switzerland) [17,18]. Baseline and clinical data from the A_1chieve cohorts were used together with economic data including annual diabetes management costs (medications and surveillance tests) and relevant co-morbid medical conditions taken from the published literature [19–22]. The costs of BIAsp30 and OGLDs were sourced from local Novo Nordisk affiliates. Both costs and effects were discounted at an annual rate of 3.0% according to World Health

Table 1 – Baseline characteristics and change in clinical outcomes after 24 weeks from the A_1chieve study in people starting BIAsp 30 + OGLDs inadequately controlled on OGLDs alone.

	Saudi Arabia	India	Indonesia	Algeria
n	901	7546	153	279
Sex, M/F (%)	66.2/33.8	63.0/37.0	62.1/37.9	49.1/50.9
Age (years)	51.0 (8.4)	50.4 (9.0)	51.2 (9.6)	57.0 (10.5)
Diabetes duration (years)	9.7 (5.5)	5.7 (3.7)	5.9 (4.7)	8.9 (6.4)
BMI (kg/m^2/change)	31.2 (5.0)/−0.3	26.0 (3.2)/−0.1	23.5 (3.5)/1.1	26.2 (4.1)/0.8
HbA_{1c} (%/change)	10.1 (1.7)/−2.70*	9.2 (1.3)/−1.9*	10.1 (1.6)/−2.90*	10.1 (2.0)/−2.60*
HbA_{1c} mmol/mol/mean change	86.9 (18.6)/−29.5*	77.0 (14.2)/−20.8*	86.9 (17.5)/−31.7*	86.9 (21.9)/−26.2*
BIAsp dose (U/day) 24 weeks/mean change from baseline	58.8 (18.9)/12.2	24.8 (7.7)/−0.6	37.5 (10.3)/12.1	45.7 (14.9)/10.2
EQ-5D/change	0.566/0.243†	0.485/0.312*	0.807/0.154*	0.673/0.152*
Systolic blood pressure (mmHg/change)	133.8 (15.3)/−6.2*	141.4 (26.7)/−10.0*	128.6 (11.6)/−5.4*	134.0 (16.2)/−2.7*
Baseline complications, *n* (%)				
Cardiovascular	317 (27.3)	1640 (23.4)	19 (12.4)	41 (14.7)
Renal	574 (49.4)	1398 (20.0)	8 (5.2)	67 (24.0)
Eye	446 (38.4)	4474 (64.0)	14 (9.2)	80 (28.7)
Foot ulcer	87 (7.5)	336 (4.8)	6 (3.9)	9 (3.2)
Neuropathy	695 (59.9)	1326 (19.0)	35 (22.9)	86 (30.8)
Lipids (mmol/L)/change				
Total cholesterol	5.3 (1.2)/−0.8*	4.5 (1.1)/0.0*	5.7 (1.1)/−0.8*	5.1 (1.3)/−0.4*
LDL cholesterol	3.2 (0.9)/−0.6*	3.2 (0.9)/−0.3*	3.4 (1.1)/−0.3	3.2 (1.3)/−0.4
HDL cholesterol	1.1 (0.2)/0.1*	1.0 (0.2)/0.0*	1.4 (0.5)/0.0	1.1 (0.4)/0.1
Triglycerides	2.2 (1.0)/−0.4*	2.0 (0.7)/−0.3*	1.8 (1.2)/−0.5*	1.7 (0.9)/−0.2
Hypoglycaemia (Events per 100 patient-years)/change				
Daytime				
Major	0.04/−0.04	0.02/−0.02	0.00/0	0.93/−0.84
Minor	0.75/+0.71	0.54/−0.40	0.85/−0.85	3.49/+1.17
Nocturnal				
Major	0.00/0	0.01/−0.01	0.00/0	1.21/−1.21
Minor	0.20/+0.19	0.23/−0.22	0.34/−0.34	2.52/−0.47

Mean (SD or %), * $p < 0.001$.

BIAsp 30, biphasic insulin aspart 30; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OGLD, oral glucose-lowering drug.

† No country-specific data available. Average is calculated from EQ-5D data of other countries from A_1chieve.

Organization (WHO) guidelines [14]. Background mortality rates for each country were taken from WHO data tables.

A short-term analysis (for the first year after starting BIAsp 30) was conducted using the incremental cost of treatment and the incremental effect on EQ-5D only.

2.3. *CORE diabetes model*

The CORE Diabetes Model is an analysis tool for both type 1 and type 2 diabetes. Independent and non-product-specific, it takes into account costs for diabetes-related therapy (acquisition costs of the insulin) and management (current clinical management activity), and complication costs (including screening and treatment strategies for micro- and macrovascular complications, and treatment practices for end-stage complications). The interactive computer simulation of disease progression is based on a series of interdependent Markov submodels that simulate the progression of diabetes-associated complications. A full description of the models has been previously published [17,18]. Each of the models applies time, health state, duration of health state, and diabetes type-dependent probabilities predominately derived from the published UKPDS, DCCT, and Framingham studies. The reliability of the model has been validated against clinical trial reports [17]. Baseline, clinical, and economic data can be entered by the user, allowing projection of country-specific short- and long-term outcomes and costs. A_1chieve study-specific change in EQ-5D HRQoL scores from the participating countries [8] replaced the default CORE values in the current analysis.

2.4. *Statistics*

Non-parametric bootstrapping was used in each simulation (1000 people and 1000 bootstraps per country) to construct confidence intervals around the data [23]. The incremental cost-effectiveness ratio (ICER) per quality-adjusted life-year (QALY) was calculated in local currency, USD, and as a fraction of the gross domestic product (GDP) per capita for each country. ICERs reveal the cost per unit of benefit from switching from one treatment to another and GDP data were taken from the World Bank report for 2011 [24]. Cost-effectiveness was pre-defined according to the WHO CHOosing Interventions that are Cost-Effective (CHOICE) programme threshold based on GDP per capita [25]. Categorisation by this system defines a health technology to be cost-effective if incremental cost per incremental QALY gained falls between 1.0 and 3.0 times GDP per capita, highly cost-effective if <1.0 GDP per capita, and dominant (i.e., cost-saving) if costs per QALY gained are <0.0.

A series of sensitivity analyses was performed to examine how robust the findings of the base-case analysis would be if the assumptions made in the model were varied. A sensitivity analysis on the time horizon was performed by extending the time horizon to 50 years, ensuring everyone was dead at the end of the study period. The impact of cost changes was examined assuming two self-measured blood glucose (SMBG) strips per day versus zero strips in the base-case; four additional visits to the healthcare practitioner in the first year following starting insulin (first visit to a specialist, others in primary care); two general practitioner visits every year after starting insulin; comparator arm starting BIAsp 30 after 5 years rather than staying on OGLDs indefinitely. The impact of HbA_{1c} changes was assessed by assuming no change in HbA_{1c} over time (+0.15%-unit increase in HbA_{1c} per year used in base-case scenario after first year), the median rather than mean change in HbA_{1c}, and the HbA_{1c} treatment effect in the quarter of the population with the smallest change. A further sensitivity analysis used average A_1chieve EQ-5D data for BIAsp 30 rather than country-specific data. For the 1-year short-term analysis, sensitivity analyses were conducted by adding the cost of monitoring strips and for four general practitioner visits, respectively.

An analysis was also conducted to project the maximum putative cost of treatment that would result in an ICER of three times GDP per capita, i.e., the limit of cost-effectiveness, to assess the room for additional costs not taken into account in the base-case analyses.

3. Results

3.1. *Life expectancy, diabetes-related complications, costs, and cost-effectiveness*

The significant improvements in surrogate clinical outcomes following change in therapy to BIAsp 30 ± OGLDs in people with T2DM (Table 1) were associated with projected improvements in life expectancy of 1.9 years in Saudi Arabia, 1.3 years in India, 1.8 years in Indonesia, and 1.5 years in Algeria.

Projected reductions in 30-year incidence of diabetes-related complications compared with OGLD treatment alone are shown in Table 2. Expressed as relative risk, the risk of a myocardial infarction event was reduced by 20% (Saudi Arabia), 19% (India), 32% (Indonesia), and 22% (Algeria). The risk of blindness was reduced by 35% in Saudi Arabia and India, 47% in Indonesia, and 33% in Algeria. The risk of dialysis was projected to fall by between 64% (India) and 78% (Indonesia), and the risk of foot ulceration by between 2% (Saudi Arabia) and 23% (Indonesia). The time free of any complication in people with T2DM was greater with BIAsp 30 ± OGLDs compared with OGLD treatment alone; the difference between treatments ranged between a gain of 2.0 years in Indonesia and 0.18 years in Saudi Arabia. Similar trends in delayed onset were observed for other complications (Table 2). The estimated QALY gains were 2.77 for Saudi Arabia, 4.57 for India, 2.73 for Indonesia, and 2.65 for Algeria.

The projected differences in glucose-lowering treatment costs, management costs, complication-related costs, and overall costs after switching therapy from OGLD only to BIAsp 30 ± OGLDs over a 30-year time horizon are shown in Table 3. While therapy costs were higher with insulin in all countries, and management costs similar, complication-related costs were lower. Accordingly, change in overall health-care expenditure ranged from 42% higher in Algeria to 4% lower in Saudi Arabia; India (+30%) and Indonesia (+20%) were intermediate. Expressed in US dollar terms, the discounted average extra cost per person ranged from cost-saving in Saudi Arabia to USD165 per year in Algeria (Table 3).

The long- and short-term cost-effectiveness of starting BIAsp 30 +/± OGLDs in insulin-naïve people with T2DM from Saudi Arabia, India, Indonesia, and Algeria is shown in Table 4. Base-case analysis (30 years) showed India, Indonesia, and Algeria to have an ICER per QALY gained of <1.0 GDP per capita (0.25, 0.47, and 0.46, respectively) compared to OGLD therapy, meeting the definition of highly cost-effective. As BIAsp 30 delivered both discounted cost savings and marked improvements in health outcomes in Saudi Arabia, the insulin therapy was cost-saving over OGLDs alone. In the short-term 1-year analysis, ICER per QALY gained after starting BIAsp 30 therapy

Table 2 – Incidence (percentage of people) and estimated time alive and free of complications (years) over 30 years after starting BIAsp 30+ OGLDs in insulin-naïve people with T2DM treated with OGLDs from Saudi Arabia, India, Indonesia, and Algeria.

	Saudi Arabia		India		Indonesia		Algeria	
	BIAsp 30	OGLD	BIAsp 30	OGLD	BIAsp 30	OGLD	BIAsp 30	OGLD
Severe vision loss								
Incidence (% people)	7.88	12.21	6.88	10.57	6.30	11.97	9.21	13.71
Time to event (years)	13.03	10.91	15.06	13.48	16.63	14.44	14.61	12.37
End-stage renal disease								
Incidence (% people)	5.57	17.23	3.37	9.43	2.69	12.37	4.73	13.67
Time to event (years)	13.51	11.39	15.50	14.05	17.11	15.14	14.97	13.30
Myocardial infarction								
Incidence (% people)	31.59	39.31	31.89	39.24	19.46	28.65	27.03	34.51
Time to event (years)	11.72	9.67	13.56	12.01	16.26	14.15	13.61	11.85
Ulcer								
Incidence (% people)	40.66	41.49	15.36	19.32	16.96	21.97	18.06	21.15
Time to event (years)	10.15	8.57	14.28	12.79	15.70	13.68	13.67	12.09

BIAsp 30, biphasic insulin aspart 30; OGLD, oral glucose-lowering drug; T2DM, type 2 diabetes mellitus.

Table 3 – Cost simulated over 30 years with BIAsp 30 + OGLDs compared with the cost of OGLD therapy.

	Saudi Arabia		India		Indonesia		Algeria	
	BIAsp 30	OGLD	BIAsp 30	OGLD	BIAsp 30	OGLD	BIAsp 30	OGLD
Total costs								
Local currency	189,473 SAR	196,760 SAR	411,046 INR	317,362 INR	290,767,442 IDR	242,748,340 IDR	1402,600 DZD	990,010 DZD
USD	49,263	51,158	7399	5713	29,077	24,275	16,831	11,880
Treatment costs								
Local currency	37,821 SAR	18,648 SAR	215,335 INR	76,114 INR	119,409,114 IDR	34,444,198 IDR	682,407 DZD	213,950 DZD
USD	9833	4848	3876	1370	11,941	3444	8189	2567
Management costs								
Local currency	39,559 SAR	35,996 SAR	55,114 INR	53,653 INR	49,563,613 IDR	47,945,153 IDR	428,538 DZD	401,841 DZD
USD	10,285	9359	992	966	4956	4795	5142	4822
Complication costs								
Local currency	112,093 SAR	142,116 SAR	140,598 INR	187,594 INR	121,795,715 IDR	160,358,989 IDR	291,655 DZD	374,220 DZD
USD	29,144	36,950	2531	3377	12,179	16,036	3500	4491

Currency conversions as of September 2013 (1 SAR = 0.26 USD, 1 IDR = 0.0001 USD, 1 INR = 0.018 USD, 1 DZD = 0.012 USD).
North Africa combined Algeria, Morocco and Tunisia, expressed in Algerian currency.
BIAsp 30, biphasic insulin aspart 30; OGLD, oral glucose-lowering drug.

was estimated to be highly cost-effective in Saudi Arabia (0.14 of GDP per capita), India (0.43), and Algeria (0.73), while being cost-effective in Indonesia (1.20 of GDP per capita) (Table 4).

3.2. *Sensitivity analyses*

The series of sensitivity analyses revealed that there was little or no impact on ICERs. This was true for extending the time horizon to 50 years, if no deterioration with time in HbA_{1c} was factored into the model, and if the median HbA_{1c} treatment effect was used in place of the mean value (Fig. 1). Similarly, there was little effect of two additional primary care visits in every year following start of BIAsp 30 or if the average global EQ-5D value replaced the country-specific data (Fig. 1). If BIAsp 30 was begun after 5 years in the OGLD group, but the model still ran for 30 years, the ICERs were projected to change only marginally in Saudi Arabia and were lower than for the base-case analysis in India, Indonesia, and Algeria (Fig. 1). The results were more sensitive to using the lowest quarter data for the HbA_{1c} treatment effect and to the inclusion of treatment costs with either additional SMBG strip use or including four additional clinic visits in the first year after the change in therapy. Nevertheless, the predicted outcomes (ICER) were still well within the cost-effective range (ICER < 3.0 ratio to GDP per capita).

The increase in total current costs that would still deliver an ICER of 3.0 GDP/QALY (i.e., which would be on the cost-effectiveness limit) was estimated to be 90% for Indonesia, 161% for Algeria, 252% for India, and 435% for Saudi Arabia.

4. Discussion

This analysis has used country-specific data for healthcare costs, combined with country-specific short-term health

Table 4 – Long-term (30-year time horizon) and short-term (1-year time horizon) cost-effectiveness of starting BIAsp 30 + OGLDs in insulin-naïve people with T2DM from Saudi Arabia, India, Indonesia, and Algeria.

	Saudi Arabia	India	Indonesia	Algeria
30-year ICER (cost per QALY gained) (base-case)				
Local currency	−2063 SAR	20,516 INR	15,710,332 IDR	155,659 DZD
USD	−550	370	1632	1955
GDP fraction	−0.03	0.25	0.47	0.46
1-year ICER (cost per QALY gained)				
Local currency	6340 SAR	35,182 INR	40,487,477 IDR	246,422 DZD
USD	1690	635	4206	3095
GDP fraction	0.08	0.43	1.20	0.73

Currency conversions as of September 2013 (1 SAR = 0.26 USD, 1 IDR = 0.0001 USD, 1 INR = 0.018 USD, 1 DZD = 0.012 USD); North Africa combined Algeria, Morocco and Tunisia, expressed in Algerian currency.
BIAsp 30, biphasic insulin aspart 30; ICER, incremental cost-effectiveness ratio; OGLD, oral glucose-lowering drug; QALY, quality- adjusted life-year; T2DM, type 2 diabetes mellitus.

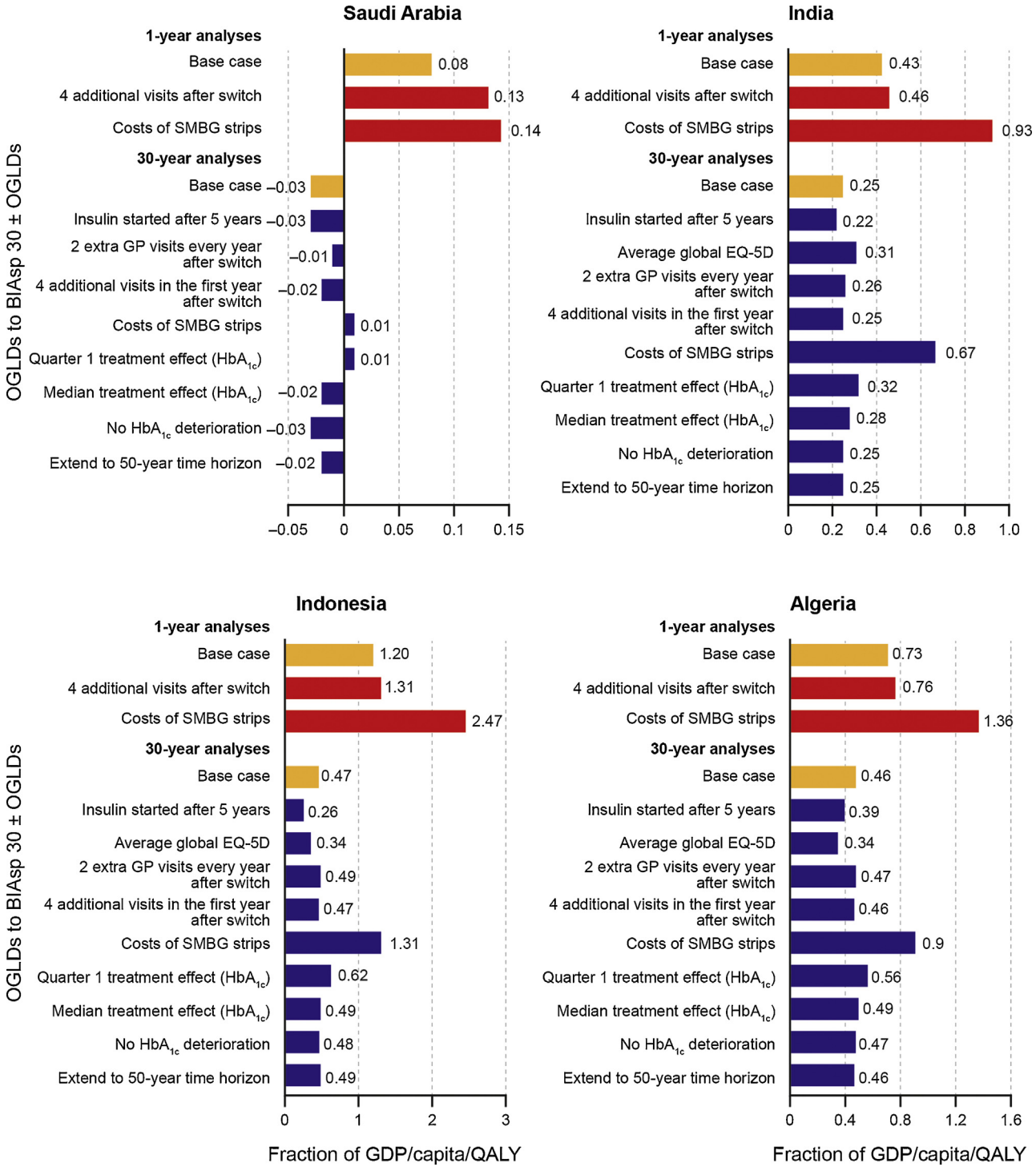

Fig. 1 – Sensitivity analysis of BIAsp 30 ± OGLDs in people with T2DM inadequately controlled on OGLDs from Saudi Arabia, India, Indonesia, and Algeria. Results presented as a fraction of GDP per capita per QALY gained. BIAsp 30, biphasic insulin aspart 30; GDP, gross domestic product; GP, general practitioner; OGLD, oral glucose-lowering drug; QALY, quality-adjusted life-year; SMBG, self-measured blood glucose; T2DM, type 2 diabetes mellitus; ICER, incremental cost-effectiveness ratio.

output data from the large A1chieve study, to estimate the long-term (base-case 30 years) costs and health outcomes associated with starting BIAsp 30 with or without OGLDs according to local practice in people with T2DM in routine diabetes care. Although the total population studied in A1chieve was large, individual country populations started on this insulin restricted the analysis to four countries (after combining data for Algeria, Morocco, and Tunisia), with large numbers of people from India and Saudi Arabia, and smaller but useful numbers from Algeria and Indonesia. These four

'countries' are very different in terms of economic resources, development, and culture, but nevertheless, when adjusted to GDP using the WHO CHOICES criteria, starting insulin therapy with BIAsp 30 was highly cost-effective by the base-case in all of them (Table 4). The positive clinical outcomes from these participants in the A_1chieve study (Table 1.) are likely to have contributed to this finding, as improved glycaemic control and HRQoL have been associated with reduced health-care costs in adults with diabetes [26,27].

Due to the chronic nature of diabetes and the severity of associated complications, diabetes is a very costly disease. These costs are not only financial, affecting, directly or indirectly, the individual and their families, in addition to social care. Studies in India indicate that the economic burden of diabetes care on families is rising rapidly, with 85–95% of all healthcare costs being borne by individuals and their families from household income [28,29]. Taking into consideration that people diagnosed with diabetes can have significantly higher healthcare requirements and expenditures than in the absence of diabetes, the growing prevalence of diabetes will pose tremendous future challenges for low to middle-income countries [30,31]. In this context, an intervention that can deliver increased life expectancy of >1 year with reduced incidence of diabetes-related complications and delayed onset of these would appear attractive.

As might be expected, costs of treatment, management, and complications were much higher in Saudi Arabia than other counties (and lowest in India) due to the economic circumstances of the country. However, the modelled extra treatment costs of starting BIAsp 30 are largely balanced out by the lower overall complication rates and, therefore, the lower estimated costs of complication management, including specific treatment costs and management costs related to those complications (Table 3). This offset effect is not complete, except in Saudi Arabia, largely because the complication costs *per se* are much lower, expressed in GDP per capita. Nevertheless, the ICERs are still all under a sixth of the WHO threshold for cost-effectiveness in the base-case. While the analysis showed cost savings in Saudi Arabia, this was not driven by differences in modelled outcomes or a larger reduction in outcomes compared to the other countries. Within the limits of the assumptions made, the numbers of people affected by adverse health events were broadly similar between the four countries, as were the improvements expected in clinical outcomes often associated with starting insulin (Table 2).

The Indonesian and Algerian data are intermediate compared with Saudi Arabia and India, Indonesian and Algerian estimates for diabetes as a proportion of total health-care expenditure being 7% and 11% of total in 2010 [32]. Both of these A_1chieve sub-populations reported relatively poor glycaemic control at baseline (mean HbA_{1c} 10.1%; 86.9 [18.6] mmol/mol) and thus had an opportunity for larger improvements at 24 weeks (−2.9%-units in Indonesia; −2.6%-units in Algeria). As HbA_{1c} is a major driver of reduced complications in diabetes, and thus in the CORE Diabetes Model, the proportionately high reductions in the cost of complications are estimated (Table 2 and 3), and the ICER associated with the intervention is highly cost-effective in GDP terms here too.

The results of the CORE modelling do not support the view, mostly from developed nations, that the costs of diabetes are driven overall by the costs of managing its complications [33]. Rather, in this analysis, they are close to being in balance. This disparity is perhaps explained by our population having T2DM and being rather older, such that death from other co-morbidities restricts the opportunity to suffer some vascular complications and to incur their costs over many years. The problem remains that, for health authorities or individuals alike, the increased cost of effective diabetes management does have to be accepted to gain savings or potential health benefits in the longer term. However, in this analysis, the short-term model, for the first year after starting BIAsp 30, based only on the incremental cost of treatment and the incremental effect on EQ-5D, indicated that an early benefit could be possible.

A number of studies have examined long-term clinical and economic outcomes after starting BIAsp 30 in western nations and in South Korea [9,10,34–36], finding it to be cost-effective. Palmer and colleagues, using data from the PRESENT study, examined the cost-effectiveness of converting from biphasic human insulin to BIAsp 30 in China. They found that the increased costs are largely offset by reduction in complication costs, but with improved outcomes giving a high level of cost-effectiveness [37]. Also of partial relevance to the current study is a cost-effectiveness analysis of conversion from biphasic human insulin to BIAsp 30 in Saudi Arabia, again based on data from the PRESENT study, which found cost savings with improved outcomes (dominance) when using the CORE Diabetes Model [28]. As well as extending this last analysis to the more typical situation of people starting insulin, in the current study the global range of HE analysis is much extended by the modelling for other countries.

The strengths and weaknesses of the underlying A_1chieve observational study data have been discussed elsewhere, limitations including the relatively short observation period, the likelihood of lifestyle change accompanying the starting of insulin therapy, and the possibility of regression to the mean in core surrogate outcomes such as HbA_{1c} [4,15]. Being an observational study, there is no control group, so we can only make HE comparisons against baseline therapy. While the intervention was still cost-effective using only HRQoL data over 1 year, it could be argued that our other sensitivity analysis, where all participants were converted to insulin at 5 years, modelled an unacceptable delay in starting insulin. The cost-effectiveness evaluations used here carry other uncertainties, such as the relevance of the underlying equations based on studies like UKPDS and the Framingham Heart Study to the populations studied in A_1chieve. However the IMS CORE Diabetes Model has been validated against a number of epidemiological and clinical studies, and country-specific epidemiological data. Furthermore, we have performed a number of sensitivity analyses, including testing fundamental assumptions such as continued deterioration with time, using a conservative measure of HbA_{1c} change, and modelling different time horizons (Fig. 1). None of these markedly affect the cost-effectiveness. The finding that the 1-year estimate, using only first-year costs and improvement in health utility based on the EQ-5D data, was also cost-effective perhaps indicates that the improvement in HRQoL makes a large contribution to the model outputs, thus reducing the impact of longer-term gains and costs. The sensitivity analysis that

otherwise most changed the ICERs was increase in use of SMBG strips, although, even here, all ICERs remained below the cost-ineffectiveness threshold.

Some uncertainties remain around health-care costs. While some were obtained from published and official sources for each country, local diabetes specialists were requested to provide values when no published data were available. Although consensus of up to three specialists was used to attempt to reduce error, some bias is inevitable. In addition, we are not able to account for changes in adherence to injection therapy in the longer term, nor rising insulin dose (and thus insulin costs) with time. For this reason, in the sensitivity analyses we explored the increase in potential overall costs that would still allow the intervention to be cost-effective at an ICER of 3.0 times GDP per capita, finding markedly higher incremental costs would be needed, leaving room for adding to the treatment costs over time.

To conclude, with the worldwide prevalence of diabetes steadily increasing and placing ever greater demand on national healthcare expenditure, policymakers need information not only on the safety and effectiveness of an intervention but also on whether it provides good value for money in relation to the cost of treatment. Using clinical data from the A_1chieve observational study, analysed using the IMS CORE Diabetes Model, our findings indicate that starting insulin therapy with BIAsp 30 in people with poorly controlled T2DM on OGLDs alone is considered to be a highly cost-effective intervention in India, Indonesia, Algeria, and Saudi Arabia. The findings are robust, being reproduced across a number of sensitivity analyses.

Conflict of interest

Asrul Akmal Shafie, Vishal Gupta, Ranya Baabbad, and Philip Home, for themselves or institutions with which they are associated, receive funding from all major international pharmaceutical companies for their advisory, lecturing, and research activities, including from Novo Nordisk. Eva Hammerby is an employee of Novo Nordisk.

Acknowledgements

We thank all the participants and investigators who helped with the A_1chieve study. The authors take full responsibility for the data and analysis supporting this article, and the results and discussion presented, but acknowledge editorial assistance from Helen Coulson of Watermeadow Medical and Last Mile P/S for assistance with analyses, funded by Novo Nordisk.

Life expectancy values reported here in each of the studied populations have been previously published in abstract form at the ISPOR 18th Annual International Meeting, New Orleans, LA, USA, May 2013 [19–22].

REFERENCES

[1] Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence in adults for 2013 and projections for 2035 for the IDF Diabetes Atlas. Diabetes Res Clin Pract 2014;103(2):137–49.

[2] International Diabetes Federation. Global guideline for type 2, diabetes. Diabetes Res Clin Pract 2014;104(1):1–52.

[3] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al., American Diabetes Association (ADA); European Association for the Study of Diabetes (EASD). Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2012;55:1364–79.

[4] Home P, Naggar NE, Khamseh M, Gonzalez-Galvez G, Shen C, Chakkarwar P, et al. An observational non-interventional study of people with diabetes beginning or changed to insulin analogue therapy in non-western countries: the A1cheive study. Diabetes Res Clin Pract 2011;94:352–63.

[5] Valensi P, Benroubi M, Borzi V, Gumprecht J, Kawamori R, Shaban J, et al., IMPROVE Study Group Expert Panel. Initiating insulin therapy with, or switching existing insulin therapy to, biphasic insulin aspart 30/70 (NovoMix 30) in routine care: safety and effectiveness in patients with type 2 diabetes in the IMPROVE observational study. Int J Clin Pract 2009;63:522–31.

[6] Davidson JA, Liebl A, Christiansen JS, Fulcher G, Ligthelm RJ, Brown P, et al. Risk for nocturnal hypoglycemia with biphasic insulin aspart 30 compared with biphasic human insulin 30 in adults with type 2 diabetes mellitus: a metaanalysis. Clin Ther 2009;31:1641–51.

[7] Fonseca V, Davidson J, Home P, Snyder J, Jellinger P, Dyhr Toft A, et al. Starting insulin therapy with basal insulin analog or premix insulin analog in T2DM: a pooled analysis of treat-to-target trials. Curr Med Res Opin 2010;26:1621–8.

[8] Shah S, Zilov A, Malek R, Soewondo P, Bech O, Litwak L. Improvements in quality of life associated with insulin analogue therapies in people with type 2 diabetes: results from the A_1chieve observational study. Diabetes Res Clin Pract 2011;94:364–70.

[9] Palmer JL, Knudsen MS, Aagren M, Thomsen TL. Cost-effectiveness of switching to biphasic insulin aspart from human premix insulin in a US setting. J Med Econ 2010;13:212–20.

[10] Valentine WJ, Palmer AJ, Lammert M, Nicklasson L, Foos V, Roze S. Long-term clinical and cost outcomes of treatment with biphasic insulin aspart 30/70 versus insulin glargine in insulin naive type 2 diabetes patients: cost-effectiveness analysis in the UK setting. Curr Med Res Opin 2005; 21:2063–71.

[11] Brod M, Cobden D, Lammert M, Bushnell D, Raskin P. Examining correlates of treatment satisfaction for injectable insulin in type 2 diabetes: lessons learned from a clinical trial comparing biphasic and basal analogues. Health Qual Life Outcomes 2007;5:8.

[12] Baik S, Chacra AR, Yuxiu L, White J, Güler S, Latif ZA. Conducting cost-effectiveness analyses of type 2 diabetes in low- and middle-income countries: can locally generated observational study data overcome methodological limitations? Diabetes Res Clin Pract 2010;88(Suppl. 1): S17–22.

[13] Shillcutt SD, Walker DG, Goodman CA, Mills AJ. Cost effectiveness in low- and middle-income countries: a review of the debates surrounding decision rules. PharmacoEconomics 2009;27:903–17.

[14] World Health Organization. Making Choices in Health: WHO Guide to Cost-Effectiveness Analysis. Geneva: World Health Organization, 2003.

[15] Shah SN, Litwak L, Haddad J, Chakkarwar PN, Hajjaji I. The A1chieve study: a 60 000-person, global, prospective, observational study of basal, meal-time, and biphasic

insulin analogs in daily clinical practice. Diabetes Res Clin Pract 2010;88(Suppl. 1):S11–6.
[16] Majeed A, El-Sayed AA, Khoja T, Alshamsan R, Millett C, Rawaf S. Diabetes in the Middle-East and North Africa: an update. Diabetes Res Clin Pract 2014;103(2):218–22.
[17] Palmer AJ, Roze S, Valentine WJ, Minshall ME, Foos V, Lurati FM, et al. Validation of the CORE Diabetes Model against epidemiological and clinical studies. Curr Med Res Opin 2004;20:S27–40.
[18] Palmer AJ, Roze S, Valentine WJ, Minshall ME, Foos V, Lurati FM, et al. The CORE Diabetes Model: projecting long-term clinical outcomes, costs and cost-effectiveness of interventions in diabetes mellitus (types 1 and 2) to support clinical and reimbursement decision-making. Curr Med Res Opin 2004;20:S5–26.
[19] Hnoosh A, Vega-Hernández G, Jugrin A, Todorova L. Direct medical costs of diabetes-related complications in Saudi Arabia. Value Health 2012;15:A178.
[20] Hnoosh A, Vega-Hernández G, Jugrin A, Todorova L. Direct medical management costs of diabetes-related complications in Algeria. Value Health 2012;15:A179.
[21] Todorova L, Hnoosh A, Bloomfield E, Shiu ML. Estimating the direct medical costs associated with diabetes-related complications in Indonesia. Value Health 2012;15:A662.
[22] Todorova L, Hnoosh A, Korde G, Shiu ML. Direct medical costs of diabetes-related complications in India. Value Health 2012;15:A662.
[23] Briggs AH, Wonderling DE, Mooney CZ. Pulling cost-effectiveness analysis up by its bootstraps: a non-parametric approach to confidence interval estimation. Health Econ 1997;6:327–40.
[24] The World Bank. World Bank Open Data. 2012. Available from: http://data.worldbank.org /(accessed02 January 2014).
[25] World Health Organization. CHOosing Interventions that are Cost-Effective (WHO-CHOICE). 2009. Available from: http://www.who.int/choice/costs/CER_thresholds/en/index.html (accessed 02 January 2014).
[26] Gilmer TP, O'Connor PJ, Rush WA, Crain AL, Whitebird RR, Hanson AM, et al. Predictors of health care costs in adults with diabetes. Diabetes Care 2005;28:59–64.
[27] Menzin J, Langley-Hawthorne C, Friedman M, Boulanger L, Cavanaugh R. Potential short-term economic benefits of improved glycemic control: a managed care perspective. Diabetes Care 2001;24:51–5.
[28] Ali M, White J, Lee CH, Palmer JL, Smith-Palmer J, Fakhoury W, et al. Therapy conversion to biphasic insulin aspart 30 improves long-term outcomes and reduces the costs of type 2 diabetes in Saudi Arabia. J Med Econ 2008;11:651–70.
[29] Ramachandran A, Ramachandran S, Snehalatha C, Augustine C, Murugesan N, Viswanathan V, et al. Increasing expenditure on health care incurred by diabetic subjects in a developing country: a study from India. Diabetes Care 2007;30:252–6.
[30] Alhowaish AK. Economic costs of diabetes in Saudi Arabia. J Family Community Med 2013;20:1–7.
[31] Soewondo P, Ferrario A, Tahapary DL. Challenges in diabetes management in Indonesia: a literature review. Global Health 2013;9:63.
[32] Zhang P, Zhang X, Brown J, Vistisen D, Sicree R, Shaw J, et al. Global healthcare expenditure on diabetes for 2010 and 2030. Diabetes Res Clin Pract 2010;87:293–301 (Erratum in: Diabetes Res Clin Pract 2011;92:301).
[33] Li R, Bilik D, Brown MB, Zhang P, Ettner SL, Ackermann RT, et al. Medical costs associated with type 2 diabetes complications and comorbidities. Am J Manag Care 2013;19:421–30.
[34] Ray JA, Valentine WJ, Roze S, Nicklasson L, Cobden D, Raskin P, et al. Insulin therapy in type 2 diabetes patients failing oral agents: cost-effectiveness of biphasic insulin aspart 70/30 vs. insulin glargine in the US. Diabetes Obes Metab 2007;9:103–13.
[35] Valentine WJ, Goodall G, Aagren M, Nielsen S, Palmer AJ, Erny-Albrecht K. Evaluating the cost-effectiveness of therapy conversion to insulin detemir in patients with type 2 diabetes in Germany: a modelling study of long-term clinical and cost outcomes. Adv Ther 2008;25:567–84.
[36] Lee KH, Seo SJ, Smith-Palmer J, Palmer JL, White J, Valentine WJ. Cost-effectiveness of switching to biphasic insulin aspart 30 from human insulin in patients with poorly controlled type 2 diabetes in South Korea. Value Health 2009;12(Suppl. 3):S55–61.
[37] Palmer JL, Gibbs M, Scheijbeler HW, Kotchie RW, Nielsen S, White J, et al. Cost-effectiveness of switching to biphasic insulin aspart in poorly-controlled type 2 diabetes patients in China. Adv Ther 2008;25:752–74.